

## ORIGINAL ARTICLE

# The importance of choice of resection procedures in T1 and T2 stage of carcinoma of the ampulla of Vater

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## Summary

**Purpose:** The ampulla of Vater (AV), with its strategic location and its remarkable predisposition to the development of various malignant tumors, makes it very challenging for surgery. In this study we aimed to examine the prognostic factors in the treatment of early-stage carcinoma of the AV as well as to contribute to the choice of optimal surgical procedure.

**Methods:** We analyzed 109 AV patients, hospitalized at the Clinical Center of Serbia from January 1999 to December 2008 and we compared the clinicopathological features, analyzed intra- and postoperative data, recurrences and survival, according to duodenopancreatectomy (DP) or local resection (LR).

**Results:** DP was performed in 83 and LR in 26 patients. Overall survival (OS) was significantly influenced by the pathological (p) tumor stage (pT1/T2 vs pT3/T4), pathological nodal stage (pN0 vs pN1), perineural and vascular invasion, grade of tumor differentiation (G1 vs G3), and resection margin status (R0 vs R1). Kaplan-Meier analysis

showed 64% 5-year overall survival of patients with pT1/T2 stage in the group with DP, and 58% in the group with LR ( $p>0.05$ ). Survival analysis of pN1 patients in these two groups showed statistically significant difference (DP 49.67 vs LR 28.68 months,  $p<0.05$ ). Postoperative complications occurred more frequently in patients treated with DP, compared with LR. Tumor recurrence occurred in 23.07% of LR patients and in 4.0% of DP patients, in pT1/T2 stage. The rate of in-hospital mortality was not significantly different in DP (9.78%) vs LR (0%) patients ( $p>0.05$ ).

**Conclusion:** Resection is mandatory for all proven AV tumors, and DP is the treatment choice. LR, due to reduced morbidity and mortality, might be recommended in elderly patients with comorbidities and in patients with stage pT1/T2, pN0 and well differentiated (G1,G2) tumors.

**Key words:** ampulla of Vater, carcinoma, duodenopancreatectomy, local resection

## Introduction

The AV is a complex functional structure formed by the joining of the pancreatic duct and the common bile duct. Various benign and malignant tumors can occur in this region, the most common being adenocarcinomas. They may arise from the pancreatic and biliary epithelium or the epithelium of the common duct [1]. In autopsy series, the incidence of cancer of AV ranged from 0.028 to 0.040%, which is 6-8% of all periamp-

ullary tumors, and less than 3% of the digestive system neoplasms [2,3]. Specific biological behavior, causing stronger local growth and less pronounced lymphatic dissemination, provides a significantly better prognosis than carcinomas of the pancreas and distal common bile duct [4]. Such biological properties coupled with earlier detection of the tumors, enable resectability rate of up to 90% [5-8]. The current research shows 5-year

overall survival rates of 30-67%. Although DP is a standard procedure in patients with malignant tumors of the AV, these tumors are still associated with high morbidity and mortality. Despite the constant development of modern surgical techniques, the rates of complications after DP are still high (35-45%). The main disadvantage of LR is a high rate of recurrence. Different studies show this rate to vary from 25 to 45%, 12-36 months post-operation [4] and based on previously acquired knowledge we conducted this investigation to examine the prognostic factors in the treatment of early-stage carcinoma of the AV and also to study the impact on survival of the different surgical procedures.

## Methods

We conducted a retrospective study and included 109 patients operated from 1/1/1999 to 12/31/2008 at the Clinic for Digestive Diseases, Clinical Center of Serbia, Belgrade. The study included patients with histologically proven adenocarcinomas originating from the AV, with no distant metastases, and treated exclusively by resection procedures. Both LR or DP were carried out in patients who had had endoscopically proven tumor of up to 20mm in diameter, and those without pancreatic tissue infiltration (pT1/T2), based on endoscopic ultrasonography examination (EUS). Tumors with diameter of more than 20mm, with EUS showing infiltration in the pancreas (pT3/T4), were treated by DP. Patients with proven adenomas, and those with tumors originating from the duodenum, pancreas or the main bile duct, with secondary infiltration of the AV were excluded from the study. Of 118 patients initially included in the study, 9 treated with DP or LR in different tumor stages were subsequently excluded, as they died within 45 days from the operation. These patients were included in the analysis of in-hospital mortality.

The data were obtained from the electronic registries of the Department of Hepatobiliary and Pancreatic Surgery, Clinic for Digestive Diseases, Clinical Center of Serbia, Belgrade, including information on demographic characteristics, tumor size, preoperative symptoms, tumor and nodal stage, perineural and vascular invasion, grade of tumor differentiation, performed surgical procedures as well as resection margin status. We subsequently analyzed morbidity, further complications, as well as in-hospital mortality, paying special attention to the analysis of prognostic factors for recurrence and long-term survival.

According to the UICC classification, TNM stage II includes pT2 and pT3 node negative tumors. Many studies [4,6-9] have shown that in pT2 and pT3 stages 20-40% of the patients have positive lymph nodes, and therefore they could be classified as N1 [4-6,9]. Further, the UICC generally puts patients with positive lymph nodes only in stage III, and does not divide them to

pT1, pT2 and pT3 tumors. Therefore, in our study, we did not classify the patients in TNM stages of disease, but we analyzed them according to the local stage of the tumor (pT stage) and especially pN stage.

The monitoring protocol consisted of regular check-ups at 3-month intervals in the first two years, followed by check-ups every 6 months, until the completion of the fifth year after surgery. Annual assessment was continued thereafter. The following parameters were registered: Ca 19-9 tumor marker estimation, laboratory parameters, endoscopic examinations and EUS after LR, and multislice computed tomography (MSCT) or magnetic resonance imaging (MRI) after DP, in order to determine the occurrence of locoregional recurrence or disseminated disease. Data on survival and quality of life were obtained with direct contact with patients or their family members.

## Statistics

Patient demographics, intraoperative factors, pathologic characteristics of the tumor and postoperative follow-up data were evaluated by Mann-Whitney U test and Cox univariate and multivariate analysis. Data on OS were analyzed with Kaplan-Meier method and differences in survival between groups were compared with log-rank test. Statistical significance was set at  $p < 0.05$ . All statistical analyses were performed with SPSS statistical package (SPSS Inc, Chicago, Ill).

## Results

The clinicopathological characteristics of patients with carcinoma of the AV are shown in Table 1.

Of 109 patients with ampullary carcinoma, DP was performed in 83 (76%) patients and LR in 26 (24%). The average age of the patients in the LR group was  $66 \pm 10.17$  years and for the DP group it was  $60 \pm 6.23$  ( $p = 0.008$ ). Men predominated (64; 59% vs 45; 41% women) ( $p > 0.05$ ). Tumor size was significantly higher in the DP group compared with the LR group ( $26 \pm 10.31$  vs  $17 \pm 8.91$  mm;  $p = 0.001$ ). Obstructive jaundice, abdominal pain, weight loss, chills and shivering, nausea and vomiting were equally present in both groups. In 9-14% of the patients there were no specific symptoms. When pT1/T2 stages were analyzed, a highly significant difference was noticed between the DP and LR groups ( $p = 0.001$ ). Patients in pT3/T4 stages were treated exclusively with DP. Tumor invasion in lymph nodes was significantly higher in the DP group compared to LR group (56.6 vs 15.3%;  $p = 0.001$ ). Perineural ( $p = 0.001$ ) and vascular invasion ( $p = 0.025$ ) were significantly more pronounced in the group of patients with DP. No statistically significant differences in the grade

**Table 1.** Clinicopathological characteristics of ampullary carcinoma

| Characteristics          | DP<br>N (%) | LR<br>N (%) | RR (95%CI)           | p value |
|--------------------------|-------------|-------------|----------------------|---------|
|                          | 83/76       | 26/24       |                      |         |
| Gender                   |             |             | 1.002 (0.385-2.607)  | 0.996   |
| Male                     | 49 (59)     | 15 (57.6)   |                      |         |
| Female                   | 34 (41)     | 11 (42.3)   |                      |         |
| Preoperative symptoms    |             |             |                      |         |
| Asymptomatic             | 8 (9)       | 3 (14)      | 0.280 (0.95-0.416)   | 0.586   |
| Abdominal pain           | 17 (20)     | 2 (9)       | 0.562 (0.557-0.349)  | 0.467   |
| Nausea or vomiting       | 26 (31)     | 5 (23)      | 0.642 (0.600-0.306)  | 0.432   |
| Obstructive jaundice     | 72 (87)     | 17 (77)     | 1.115 (0.318-0.216)  | 0.271   |
| Weight loss              | 34 (41)     | 8 (36)      | 0.245 (0.808-0.405)  | 0.623   |
| pT stage                 |             |             | 3.434 (1.792-5.979)  | 0.001   |
| T1/T2                    | 50 (60.3)   | 26 (100)    |                      |         |
| T3/T4                    | 33 (39.7)   | 0           |                      |         |
| pN stage                 |             |             | 8.269 (2.270-30.119) | 0.001   |
| N0                       | 36 (43.4)   | 22 (84.6)   |                      |         |
| N1                       | 47 (56.6)   | 4 (15.3)    |                      |         |
| Tumor invasion           |             |             |                      |         |
| Perineural               | 27 (32.5)   | 1 (4.5)     | 10.125 (1.293-7.280) | 0.001   |
| Vascular                 | 34 (41.0)   | 3 (13.6)    | 4.395 (1.205-16.026) | 0.025   |
| Lymphatic                | 49 (59.0)   | 6 (27.3)    | 3.843 (1.365-10.821) | 0.011   |
| Grade of differentiation |             |             |                      |         |
| G1                       | 37 (44.5)   | 12 (46.1)   | 0.938 (0.388-2.272)  | 0.888   |
| G2                       | 41 (49.3)   | 9 (34.6)    | 0.844 (0.738-4.606)  | 0.190   |
| G3                       | 5 (6.01)    | 5 (19.2)    | 0.269 (0.071-1.018)  | 0.053   |
| Resection margins        |             |             | 0.868 (0.217-3.467)  | 0.841   |
| R0                       | 73 (88.0)   | 22 (84.6)   |                      | NS      |
| R1                       | 10 (12.0)   | 4 (15.3)    |                      |         |
| Tumor recurrence         |             |             |                      |         |
| Yes                      | 4 (4.8)     | 6 (23.1)    | 6.288 (0.028-0.585)  | 0.003   |
| No                       | 79 (95.2)   | 20 (76.9)   |                      |         |

DP: duodenopancreatectomy, LR: local resection, RR: R0 and R1 resection margins, NS: non significant

of differentiation between the two study groups were noticed. Most patients had well differentiated-G1 and moderately differentiated-G2 tumors. Positive surgical margin was more frequently present in the LR group (15.3%) than in the DP group (12.00%), but the difference was not statistically significant ( $p=0.841$ ). Disease recurrence was significantly more prevalent after LR (23.1%) than after DP (4.8%;  $p=0.003$ ).

#### Operative data analysis

Data related to the operation and the postoperative period are shown in Table 2.

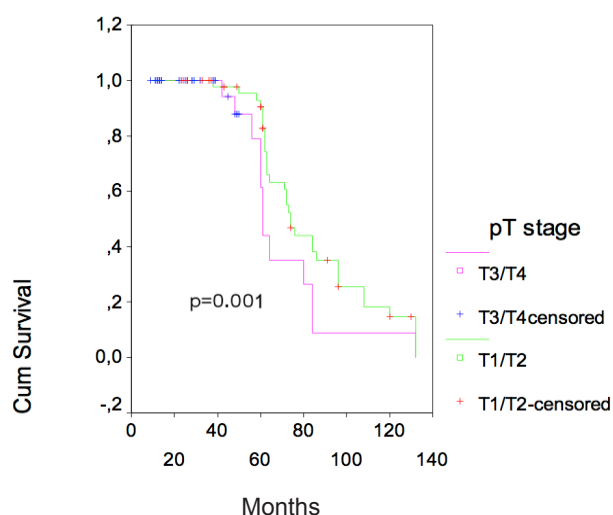
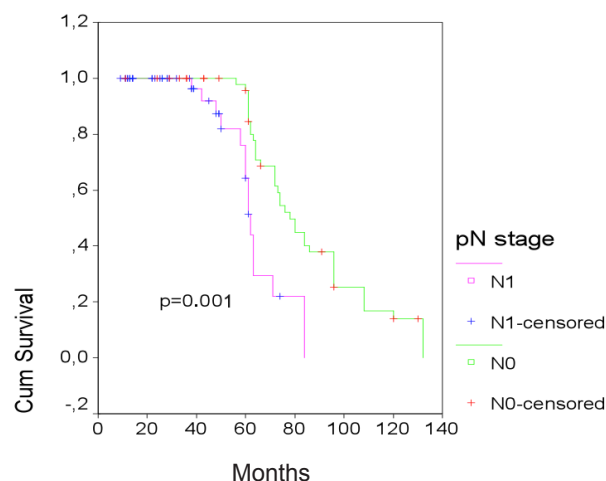
The mean blood loss was significantly higher

in patients who underwent DP compared with LR (680 vs 360 ml;  $p=0.009$ ). The duration of operation was longer in the DP group compared with LR (340 vs 170 min;  $p=0.046$ ). The incidence of pancreatic fistula was higher in patients with DP (31.3%) compared with LR (0%);  $p=0.040$ ). The occurrence of biliary fistula was not significantly different between the two groups (DP 3.6 vs LR 7.7% ;  $p=0.397$ ). Bleeding and abdominal abscess were significantly more frequent in the DP group of patients (15.7 and 18%) than in the LR group (0%;  $p=0.032$  and  $p=0.020$ ). Delayed gastric emptying was registered only in the DP group (in 16.8% of the patients).

**Table 2.** The intra- and postoperative data of ampullary carcinoma

| Variables                         | DP<br>N (%)   | LR<br>N (%)   | RR (95%CI)          | p value |
|-----------------------------------|---------------|---------------|---------------------|---------|
| Blood loss (ml) (range)           | 680 (70-106)  | 360 (270-520) | 1.000 (0.635-10.67) | 0.009   |
| Length of operation (min) (range) | 340 (230-480) | 170 (130-385) | 1.000 (0.586-1.987) | 0.046   |
| Postoperative complications       |               |               |                     |         |
| Pancreatic fistula                | 26 (31.3)     | 0             | 0.687 (0.594-0.794) | 0.040   |
| Biliary fistula                   | 3 (3.6)       | 2 (7.7)       | 0.450 (0.071-2.852) | 0.397   |
| Bleeding                          | 13 (15.7)     | 0             | 1.186 (1.081-1.301) | 0.032   |
| Abdominal abscess                 | 15 (18.0)     | 0             | 1.221 (1.103-1.350) | 0.020   |
| Delayed gastric emptying          | 14 (16.8)     | 0             | /                   | /       |
| Postoperative mortality           | 9 (9.78)      | 0             | 1.122 (1.041-1.209) | 0.080   |

For abbreviations see footnote of Table 1

**Figure 1.** Kaplan-Meier survival curves according to the pT stage**Figure 2.** Kaplan-Meier survival according to pN stage.

### Survival analysis

The rate of in-hospital mortality in the DP group (9 of 92 patients/9.78%) was not statistically different from the group with LR (0%;  $p=0.080$ ).

Table 3 shows the univariate Cox regression analysis of patient overall survival.

Patients who underwent surgery in early stage pT1/T2 lived significantly longer compared to patients in the pT3/T4 stage (70.08 vs 38.44 months; Figure 1;  $p=0.001$ ). Patients who had no lymph node invasion (pN0) lived significantly longer compared to the patients with lymph node invasion (pN1) (74.89 vs 39.10 months; Figure 2;  $p=0.001$ ). Patients who underwent surgery and had tumor-free resection margin (R0), had significantly longer survival than the patients with histologically confirmed tumor infiltration on

the resection line (R1) (60.68 vs 32.73 months; Figure 3;  $p=0.001$ ). Perineural invasion (31.11 vs 66.84 months), lymphatic (41.67 vs 75.64) and vascular invasion (33.30 vs 69.03;  $p=0.001$ ) also significantly contributed to shorter OS. When the groups of patients with well and poorly differentiated tumors (G1/G3) (65.08 vs 34.92 months) were compared, a statistically significant difference concerning OS emerged (Figure 4;  $p=0.002$ ). Patients with DP lived longer than patients with LR (76.91 vs 62.88 months) but this difference was not statistically significant ( $p=0.536$ ).

Table 4 shows the OS (median and > 5 years) in various tumor stages, depending on the resection margin status, analyzed between the DP and LR groups.

There was no statistically significant dif-

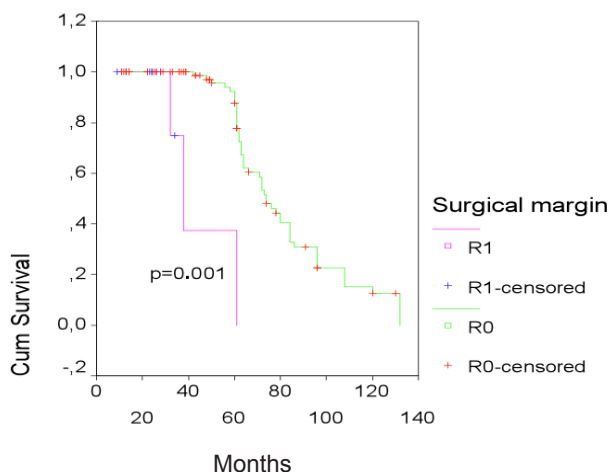
**Table 3.** Univariate Cox regression analysis of clinicopathological characteristics of tumor affecting overall survival

| Characteristics          | N (%)                  | Survival (months)<br>Mean±SD | RR (95%CI)            | p value |
|--------------------------|------------------------|------------------------------|-----------------------|---------|
| Tumor size (cm)          |                        |                              |                       |         |
| > 2                      | 64 (58.7)              | 56.34±32.885                 | 0.798 (1.6842-7.538)  | 0.451   |
| ≤ 2                      | 45 (41.3)              | 60.68±26.978                 |                       |         |
| T stage                  |                        |                              |                       |         |
| T1/T2                    | 76 (69.7)              | 70.08±28.215                 | 5.187 (22.578-43.151) | 0.001   |
| T3/T4                    | 33 (30.3)              | 38.44±25.518                 |                       |         |
| N stage                  |                        |                              |                       |         |
| N0                       | 58 (53.3)              | 74.89±28.121                 | 2.046 (26.113-45.468) | 0.001   |
| N1                       | 51 (46.7)              | 39.10±20.961                 |                       |         |
| Resection margins        |                        |                              |                       |         |
| R0                       | 95 (87.2)              | 60.68±30.07                  | 1.142 (13.085-47.319) | 0.001   |
| R1                       | 14 (16.8)              | 32.73±23.72                  |                       |         |
| Tumor invasion           |                        |                              |                       |         |
| Perineural               |                        |                              | 5.932 (21.973-45.501) | 0.001   |
| Yes                      | 29 (26.6)              | 31.11±21.687                 |                       |         |
| No                       | 80 (73.4)              | 66.84±28.496                 |                       |         |
| Lymphatic                |                        |                              | 5.005 (24.042-43.893) | 0.001   |
| Yes                      | 56 (51.3)              | 41.67±28.783                 |                       |         |
| No                       | 53 (48.6)              | 75.64±22.347                 |                       |         |
| Vascular                 |                        |                              | 5.463 (20.898-42.566) | 0.001   |
| Yes                      | 38 (34.8)              | 33.30±22.131                 |                       |         |
| No                       | 71 (65.1)              | 69.03±28.916                 |                       |         |
| Grade of differentiation |                        |                              |                       |         |
| G1 vs G2                 | 49 (44.9)<br>50 (45.8) | 65.08±32.153<br>55.02±29.376 | 0.989 (2.801-22.013)  | 0.124   |
| G2 vs G3                 | 50 (45.8)<br>10 (9.1)  | 55.02±29.376<br>39.15±18.823 | 0.997 (1.538-33.278)  | 0.049   |
| G1 vs G3                 | 49 (45)<br>10 (9.1)    | 65.08±32.153<br>34.92±15.173 | 9.230 (1.700-48.614)  | 0.002   |
| Surgical procedure       |                        |                              |                       |         |
| DP                       | 83 (76)                | 76.91±20.286                 | 0.245 (0.481-1.575)   | 0.536   |
| LR                       | 26 (24)                | 62.88±15.879                 |                       |         |

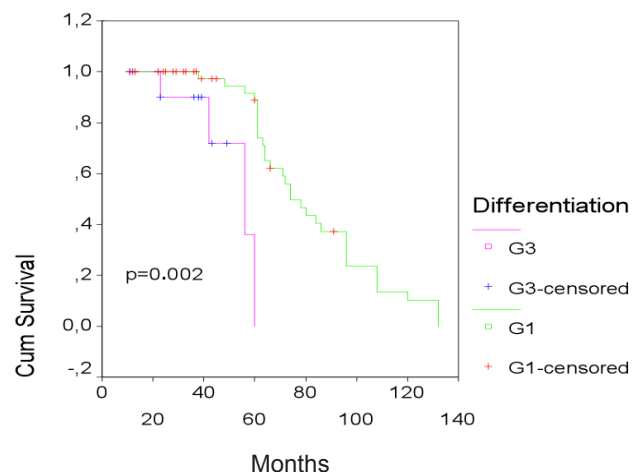
For abbreviations see footnote of Table 1

ference in OS (median) among patients in pT1/T2 stage treated by DP and LR (76.35 vs 74.21 months;  $p=0.154$ ). Patients who had been pre- or intraoperatively classified as T3 or T4 stage of disease, were not treated with LR, but only with DP. By analyzing median and 5-year OS between the patients with early stage pT1/T2 and patients with pT3/T4 stage, which were treated exclusively by DP, a significant survival benefit was shown in patients with early-stage disease (76.35 vs 38.44 months,  $p=0.01$ ). Comparing survival of patients with no nodal involvement (pN0), no statistical-

ly significant differences were noticed among patients treated with DP vs LR (77.13 vs 64.47;  $p=0.135$ ). However, N1 patients with DP lived significantly longer than patients treated with LR (49.67 vs 28.68 months;  $p=0.010$ ). Analysis of the influence of resection margin status on survival showed that there was no statistically significant difference between patients with DP vs LR, when the margins were tumor-free (R0) (71.12 vs 63.0 months;  $p=0.576$ ). Patients with neoplastic invasion of the resection margin (R1) had shorter survival compared to those with R0, but there were



**Figure 3.** Kaplan-Meier survival according to surgical margin.



**Figure 4.** Kaplan-Meier survival according to grade of differentiation.

**Table 4.** The impact of tumor stage, nodal stage, and surgical margin status on survival in DP and LR

| Variables        | DP<br>Months<br>Mean±SD | LR<br>Months<br>Mean±SD | RR (95% CI)<br>Months | p value |
|------------------|-------------------------|-------------------------|-----------------------|---------|
| T stage          |                         |                         |                       |         |
| T1 /T2           | 76.35±27.452            | 74.21±12.473            | 0.965 (65.01-79.42)   | 0.154   |
| T3 /T4           | 38.44±25.518            | /                       | /                     | /       |
| N stage          |                         |                         |                       |         |
| N0               | 77.13±20.926            | 64.47±20.173            | 1.213(0.879-1.435)    | 0.135   |
| N1               | 49.67±14.154            | 28.68±21.361            | 1.210 (1.214-298)     | 0.010   |
| Surgical margins |                         |                         |                       |         |
| R0               | 71.12±32.263            | 63.00 ±15.846           | 0.768 (0.510-0.926)   | 0.576   |
| R1               | 45.67 ±32.263           | 38.91±20.286            | 0.457 (0.781-1.742)   | 0.786   |

For abbreviations see footnote of Table 1

no significant difference between the two operative procedures (45.67 vs 38.91 months; p=0.786).

Table 5 shows the occurrence of relapses in different tumor stages and depending on the resection margin status between DP and LR.

In pT1/T2 stage, relapse was confirmed in 4.0% of the patients with DP and in 23.07% of the patients with LR (p=0.022). In N0 stage there was no statistically significant difference in the recurrence of disease between the two surgical procedures (5.55 vs 13.76%; p=0.166). But in the group with positive lymph nodes, recurrence was

significantly more frequent after LR compared to DP (75.0 vs 4.25%; p=0.002). Analysis of relapses in patients with positive surgical margins (R1) showed that they were significantly more prevalent in patients after LR (75 vs 20%; p=0.040). Multivariate logistic regression analysis showed that in the early disease stages, pN stage (N1) and the status of resection margins (R1) were associated with 1.119 and 3.083-fold increased risk for disease recurrence in the LR group, compared with DP group (p=0.002).

**Table 5.** The impact of tumor stage, nodal stage and surgical margins status on tumor recurrence in DP and LR

| Variables        | DP<br>N (%) | LR<br>N (%)  | RR (95%CI)           | p value |
|------------------|-------------|--------------|----------------------|---------|
| T stage          |             |              |                      |         |
| T1 /T2           | 2/50 (4.00) | 6/26 (23.07) | 5.769 (0.026-0.4748) | 0.022   |
| T3 /T4           | 2/33 (6.06) | 0            | /                    | /       |
| N stage          |             |              |                      |         |
| N0               | 2/36 (5.55) | 3/22 (13.76) | 0.276 (0.041-1.866)  | 0.166   |
| N1               | 2/47 (4.25) | 3/4 (75)     | 1.119 (0.001-50.214) | 0.002   |
| Surgical margins |             |              |                      |         |
| R0               | 2/73 (2.73) | 3/22 (13.76) | 0.517 (0.082-3.251)  | 0.475   |
| R1               | 2/10/ (20)  | 3/4/ (75)    | 3.083 (0.009-1.294)  | 0.040   |

For abbreviations see footnote of Table 1

## Discussion

Ampullary carcinomas are rare compared to the other malignancies of the digestive tract. Due to the disease extension (bulky disease), important data on surgical treatment of tumors of the AV are insufficient. Surgical radicality and potential curability of DP in the treatment of AV are crucial factors to be achieved. Indications for LR are a long-lasting subject of debate. LR is proposed as a method of choice in ampullary tumors with diameter less than 2 cm; in tumors with severe dysplasia or in low-risk villous adenoma; in the case of carcinoma *in situ* (Tis); adenocarcinoma in stage pT1N0M0/G1-G2; in elderly patients with associated chronic diseases who are at high risk for extensive surgery such as a DP; and in patients who refuse DP [10]. Beger et al. suggest LR with obligatory removal of lymph nodes of the front and back of the head of pancreas and supraduodenal nodes [11].

There are various problems concerning the diagnosis and accurate preoperative assessment of the stage of disease. On endoscopic biopsy more than 40% of the tumors are interpreted as adenoma, with the definitive histological diagnosis being adenocarcinoma [12,13]. The total accuracy of EUS in staging varies from 62 to 95%. Sensitivity, specificity and accuracy of EUS in detecting nodal invasion are 61, 100 and 84%, respectively, compared with CT (33, 92 and 68%, respectively) [11,15].

Until 15 years ago, DP was associated with mortality rates of over 20%. With the development of modern surgical techniques and with the introduction of postoperative monitoring, mortality rate in large centers dropped to 2- 5% [3,16-

18]. The results of our study have shown in-hospital mortality of 9% after DP and 0% after LR.

Despite the significantly reduced mortality rate, postoperative complications after DP remain high, and their incidence was reported to be up to 45%. In our study, the incidence of postoperative complications after performing DP was 31%, which was significantly higher than the one observed after LR (8.0%).

The high rate of tumor recurrence can be a consequence of incomplete LR. Different studies showed recurrence rates after LR of 25 to 45%, 16-35 months postoperatively [13,14,19]. Winter et al. reported 20% local recurrences after LR [4]. Branum and Lindell showed extremely high rates of recurrence after LR (75 and even 80%), but in a small series of patients [20,21]. Feng et al. found a relapse rate of 48% in patients after LR [22]. Of the 5 patients with LR in the study of Sperti et al., 3 developed local relapse [23]. Park et al. claimed that the presence of lymph node metastasis is the most significant factor for tumor recurrence [24]. However, Carter et al. showed that lymphovascular invasion, perineural invasion, stage and pancreaticobiliary subtype predicted survival in a multivariate model analysis [25].

In our study, relapse occurred in 23.07% (6/26) of the patients after LR, 1-3 years postoperatively. In 3 patients the relapse was local and subsequently the patients underwent DP. In the other 3 patients we confirmed dissemination of disease and they were treated with palliative procedures, but died within 4-7 months. In the pT1/T2 DP group relapse occurred in 4% (2/50) of the patients, and in pT3/T4 stage in 6.06% (2/33). All patients had proven systemic disease and were subsequently treated with chemotherapy and

symptomatic therapy. In our patients, disease recurrence was significantly depended on the presence of nodal disease (N1) and presence of tumor at the resection line.

Analysis of survival after LR and after DP is very important [25]. Lindell et al. have shown that the 5-year OS rate after DP was 35%, while it was only 10% after LR [21]. In the Feng et al. study, the rate of 5-year OS in the DP group was 53.5% and in the LR group 48.0% [22]. Barauskas et al. reported OS rate of 92% in the early stages of disease (pT1/T2) [9] and de Castro et al. reported 5-year OS rate of 75% after LR and 5-year OS after DP of 38% [26]. Di Giorgio et al. showed 5-year OS rate of 64.6% after DP [13] and Nikfarjam et al. reported that LR was a suitable alternative to PD in patients with pT1 and pT2 adenocarcinomas [27].

In our study, median survival in pT1/T2 stage after DP was 76.35 months and 74.21 months after LR, and there was no significant difference in 5-year OS between DP and LR (64 vs 58%;  $p=0.154$ ). Survival was positively and significantly influenced by

early tumor stage, negative nodal status, absence of perineural invasion, R0 resection margins and good tumor differentiation (G1,G2).

## Conclusions

Due to lower morbidity and mortality, LR should be considered as a reasonable alternative in elderly patients with significant comorbidities, as well as in those who refuse DP. In the early stages of disease, without nodal invasion, and with well-differentiated tumors, LR can provide long survival that does not differ significantly from the one observed in DP.

However, it is not easy to accurately determine the stage of disease, neither the grade of tumor differentiation preoperatively. In pT1 and pT2 stages, nodal invasion is confirmed in 10-28% of operated patients. Nodal invasion and positive resection margins significantly affect relapse. Because of that, DP should be the first treatment option in the treatment of all AV tumors.

## References

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